II. REMARKS

FORMAL MATTERS:

Claims 1-10, 15, 20, and 25-60 are pending after entry of the amendments set forth herein.

Claims 1-10, 15, 20, 25-39, and 52-54 were examined. Claims 1-10, 15, 20, 25-29, and 32-39 were rejected. Claims 52-54 were objected to. Claims 30 and 31 were allowed. Claims 40-51 were withdrawn from consideration.

The specification is amended to add the cross-reference to earlier-filed applications, insert sequence identifiers, and correct obvious errors.

Claims 10, 15, 20, and 52-54 are amended. The amendments to claims 10, 15, 20, and 52-54 were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claims 10, 15, 20, and 52-54 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations of US 2005/0244406: claims 10, 15, and 20: paragraphs 0115, 0117, and 0118; and paragraphs 0083 and 0084; claims 52-54: paragraphs 0083 and 0084. New claims 55-60 find support throughout the specification and, for example, in the claims as originally filed, see, e.g., claims 10, 15 and 20. Accordingly, no new matter is added by the amendments to claims 10, 15, 20, and 54.

No new matter is added.

SEQUENCE COMPLIANCE

The Office Action sates that the sequence listing filed May 5, 2005, does not provide for the peptide PDYGHYDDKDTLDLNTPVDKT described on page 46, line 21 of the specification and referred to as "PEPI."

Applicant notes that the above-noted sequence is included in the Sequence Listing as SEQ ID NO:35.

Applicant respectfully requests entry of the above-noted amendment to the specification, which amendment identifies the sequences as SEQ ID NO:35.

SPECIFICATION

The Office Action requested that the priority information be updated in the specification.

Applicant respectfully requests entry of the above-noted amendment to the specification, requesting insertion of priority data information.

OBJECTIONS TO THE CLAIMS

Claims 52-54 were objected to. The Office Action stated that claims 52-54 recite "wherein the antibody reduces or inhibits the binding of C5a to C5aR"; and objected to "the absence of a clear recitation of the antigen specificity of the claimed antibodies."

Without conceding as to the correctness of this objection, claims 52-54 are amended to recite "wherein the antibody binds to C5aR and reduces or inhibits the binding of C5a to C5aR."

Applicant submits that the objection to claims 52-54 has been adequately addressed. The Examiner is thus requested to withdraw the objection.

REJECTIONS UNDER §112, ¶1

Claims 10, 15, and 20 were rejected under 35 U.S.C. §112, first paragraph. Claims 31, 35, and 36 were rejected under 35 U.S.C. §112, first paragraph. Claims 5, 8, and 29 were rejected under 35 U.S.C. §112, first paragraph.

Claims 10, 15, and 20; written description

The Office Action stated that the specification does not contain a written description of the claimed invention, and stated that the disclosure does not reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Applicant respectfully traverses the rejection.

Requirements to satisfy the written description requirement of 35 U.S.C. §112, first paragraph

The Guidelines for examination of patent applications under the 35 U.S.C. §112, first paragraph, ("Written Description" Requirement) are set out in the MPEP §2163, and provide instructions for examining patent applications for compliance with the written description requirement of 35 U.S.C.§112, first paragraph.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

The Written Description Guidelines state:

(1) There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed[1];

[1] MPEP §2163(I)(A) and MPEP §2163(II)

(2) The Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims[2];

(3) Consequently, rejection of an original claim for lack of written description should be rare[3];

(4) An Examiner should review the entire application to understand how Applicant provides support for the claimed invention[4];

(5) Such a review is conducted *from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art* (emphasis added)[5]; and

(6) an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention[6].

As stated in the Written Description Guidelines, "In most technologies which are mature, and *wherein the knowledge and level of skill in the art is high*, a written description question **should not be raised** for original claims even if the specification discloses only a method of making the invention and the function of the invention."[7] The Written Description Guidelines are based in part on *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir.1997). It should be remembered that *University of California v. Eli Lilly and Co.*, (Fed. Cir.1997) was based on a patent that was filed in 1977, i.e., over 30 years ago, when the level of skill in the art was not at the level that it was as of the filing date of the instant application.

The Written Description Guidelines state that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species; and that a "representative number of species" means that the species which are adequately described are representative of the entire genus. The Written Description Guidelines state that there may be situations in which one species adequately supports a genus; and that what constitutes a "representative number" is an inverse function of the skill and knowledge in the art.[8]

[2] MPEP §2163(II)(A)
[3] MPEP §2163(II)(A)
[4] MPEP §2163(II)(A)(2)
[5] MPEP §2163(II)(A)(2).
[6] MPEP §2163(II)(A)(3)(a)
[7] MPEP §2163(II)(A)(3)(a)(i)
[8] MPEP §2163 (II)(A)(3)(a)(ii).

The Federal Circuit explained that examples are not necessary to support the adequacy of the written description, and that the written description standard may be met even where actual reduction to practice of an invention is absent[9].

The instant specification provides adequate written description.

The instant specification describes antibodies that are reactive with an extracellular loop of C5aR and that inhibit C5a binding toC5aR. The instant specification provides working examples of three different monoclonal antibodies that bind C5aR and inhibit binding of C5a to C5aR. Amino acid sequences of heavy and light chains of the antibodies were determined, and the epitopes recognized by the antibodies were characterized.

Antibodies are well-studied polypeptides, and the skill level and knowledge in the field of antibodies and generation of antibody variants is very high. Amino acid sequences of antibody heavy and light chains can be modified using standard methods well known to those of ordinary skill in the art. Specification, paragraphs 0096-0106, and paragraphs 0115-0145. The instant specification provides detailed information as to the specificity of the antibodies, and also provides information as to how to determine whether an antibody (e.g., an antibody of claim 10, 15, or 20) would have activity recited in claims 10, 15, and 20, e.g., whether an antibody inhibits binding of C5a to C5aR. Specification, paragraphs 0109-0110.

As noted above, the Written Description Guidelines state that there may be situations in which one species adequately supports a genus; and that what constitutes a "representative number" is an inverse function of the skill and knowledge in the art.[10] Given the working examples provided in the instant specification, and given the skill level and knowledge in the field, those skilled in the art would recognize that Applicant had possession of the invention as recited in claims 10, 15, and 20.

Nevertheless, and solely in the interest of expediting prosecution, claims 10, 15, and 20 are amended to recite "95%" amino acid sequence identity, and to recite "wherein the antibody binds to C5aR."

Claims 31, 35, and 36; enablement

The Office Action stated that the deposit of 12D4-N17 is not sufficient to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, for the deposit of biological materials.

[9] *Falkner v. Inglis* (448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006)
[10] MPEP §2163 (II)(A)(3)(a)(ii).

Applicant notes that claim 31 recites ECACC accession number 02090226, which corresponds to the 6C12 cell line. Applicants further note that claims 35 and 36 recite a conjugate. As such, it appears that inclusion of claims 31, 35, and 36 in this rejection was in error.

Applicant notes that claim 32 recites ECACC accession number 04090801, which corresponds to the 12D4 cell line. Applicants presume that the Office meant this rejection to apply to claim 32, and will respond accordingly.

Applicant provides herewith a Statement of Availability of Biological Deposit, which statement confirms that: 1) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent on the application; and 2) that the deposit of the hybridoma having the accession number 04090801 produces the antibody 12D4, as described in the instant application.

Claims 5, 8, and 29; new matter

The Office Action stated that the specification as originally filed does not provide support for "accession number 04090801."

As discussed above, Applicant provides herewith a Statement of Availability of Biological Deposit, which statement confirms that the deposited cell line produces the antibody 12D4, as described in the above referenced patent application. It is Applicant's understanding that such a statement will adequately address this rejection.

Specification

The Office Action objected to the specification as including new matter.

It is Applicant's understanding that such the above-discussed Statement of Availability of Biological Deposit will adequately address this objection.

REJECTIONS UNDER §103(A)

Claims 1-9, 25-28, and 33-39 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Morgan et al. (U.S. Patent No. 5,480,974; "Morgan") in view of Cain et al. ((2001) *Biochem. Pharmacol.* 61:1571; "Cain"), Crass et al. ((1999) *J. Biol. Chem.* 274:8367; "Crass"), Opperman et al. ((1993) *J. Immunol.* 151:3785; "Opperman), and Pease et al. ((1994) *Eur. J. Immunol.* 24:211; "Pease"). Applicant respectfully traverses the rejection.

Morgan

Morgan discusses an antibody that binds to a peptide from the N-terminus of C5aR (residues 9-29). Morgan neither teaches nor suggests production of antibodies to extracellular loops of C5aR other than the N-terminal domain.

The Office Action stated that Morgan teaches making and using C5aR-specific antibodies, including antagonistic antibodies. However, the N-terminus-specific antibody exemplified in Morgan was effective in neutralizing chemotaxis of neutrophils only at very high concentrations. Maximum inhibition of neutrophil chemotaxis required 800 µg/ml of the antibody (see Morgan, column 19, line16). In contrast, only 1.5 µg/ml of mAb 7F3 was required to completely inhibit chemotaxis of neutrophils (see Figure 5 in the instant application).

Morgan neither teaches nor suggests production of antibodies to extracellular loops of C5aR other than the N-terminal domain; and, given the poor results with the one antibody tested for inhibition of neutrophil chemotaxis, Morgan does not provide any motivation to make antibodies to any other region of C5aR.

None of the secondary references cures the deficiencies of Morgan.

Oppermann

The Office Action stated that Oppermann provides for identification of C5aR binding sites, including information describing extracellular loops other than the N-terminal domain.

Oppermann discusses antibodies raised against various domains of C5aR. In particular, antibodies were raised against the following:

- the N-terminal domain - "anti-Ex1 antibodies"
- the first extracellular loop - "anti-Ex2 antibodies"
- the second extracellular loop - "anti-Ex3 antibodies"
- the third extracellular loop - "anti-Ex4 antibodies".

Oppermann Table IV (page 3790) shows results of experiments to assess the ability of these antibodies to inhibit binding of C5a to C5aR. Oppermann Table IV shows that **only EX1-specific antibodies** (i.e. antibodies directed against the **N-terminal domain**) were capable of inhibiting C5a binding to C5aR. Indeed, Oppermann clearly does not consider antibodies directed to the other extracellular loops to be capable of inhibiting binding of C5a and C5aR. See, for example, the following statements made throughout the paper:

"These results imply that an amino acid sequence rich in aspartate within the receptor aminoterminus represents both an immunodominant epitope and a ligand binding site on the C5aR" (Oppermann, Abstract, emphasis added).

"As shown in Table IV the pretreatment of PMN with EX1-specific polyclonal antibodies reduces binding of C5a-F by 75%. In contrast, antibodies with specificities for the extracellular domains EX2, EX3 and EX4 did not interfere with C5a binding to its receptor." (Oppermann, emphasis added, page 3790, first paragraph, right hand column).

"This treatment significantly reduced the binding of antibodies specific for the EX1 domain (Table III). In contrast, epitopes on the other extracellular oriented domains of the C5aR were still accessible to the respective antibodies." (Oppermann, emphasis added, page 3790, last paragraph, right hand column).

"The preabsorption of C5aR on PMN with polyclonal antibodies against its extracellular domains EX2, EX3 or EX4 did not inhibit C5a binding, nor did the preabsorption of receptors with an excess of C5a prevent the binding of these antibodies to cells. The extracellular loops EX2, EX3 or EX4 therefore appear not to contain essential ligand binding sites. In contrast, C5a and anti-EX1 mAb and polyclonal antibodies mutually interfered with their binding to the C5aR." (Oppermann, emphasis added, page 3792, first full paragraph, right hand column).

Oppermann teaches that C5aR extracellular loops 1, 2 and 3 do not contain essential ligand binding sites. Oppermann therefore teaches away from instant claims 1-9, 25-28, and 33-39, which relate to antibodies specific extracellular loops of C5aR other than the N-terminal domain, which antibodies reduce or inhibit C5a binding to C5aR.

Pease

The Office Action stated that Pease provides for the identification of C5a receptor binding sites.

Pease discusses chimeric C5aR/fMLP receptors in which extracellular domains of the C5a receptor were substituted with corresponding domains of the formyl peptide receptor. Pease concludes that the first extracellular loop of C5aR was not involved in ligand binding but that the N-terminus and the second and third extracellular loops **may** be involved because replacing these regions abolished C5a binding. An alternative explanation offered by Pease was that the failure of the chimeric constructs to bind C5a was due to disruption of the receptor's conformation/structure rather than removal of an actual C5a binding site; e.g. in chimera #3 a potential N-linked

glycosylation site was introduced into the second extracellular loop. Pease, page 214, column 2, first paragraph. As such, Pease does not conclusively identify non-N-terminal extracellular loops as being involved in C5a binding. At best, Pease was able to conclude that the role of the amino terminus and extracellular loops two and three in ligand binding "cannot be excluded." Pease, page 214, column 2, under "Concluding remarks."

There is no disclosure in Pease of antibodies generated against the extracellular loops of C5aR.

Crass

The Office Action stated that Crass teaches that the second extracellular loop is critically involved in the two-site model for the human C5a receptor.

Crass describes C5aR/C3aR chimeric receptors which were tested for binding of C5a and activation of downstream signalling. Replacing the C5aR N-terminus with C3aR N-terminal domain (construct Ch8) reduced C5a binding by >1000 fold, supporting the notion that the N-terminus is the most important ligand binding site since disrupting it completely abolished C5a binding. The inverse construct (Ch9: C5aR N-terminus on C3aR) had binding of C5a with a KD ~6 fold lower than on wildtype C5aR but also some signal transduction, suggesting that C5a could bind poorly (compared with C3a) to the transmembrane (TM) core and 2nd loop in C3aR and effect signalling. These results support the N-terminus as being the most important site to inhibit.

It is interesting to note that construct Ch11 (C5aR-N- terminus and C5aR second loop on C3aR) had even better binding of C5a than Ch9 (KD nearer to wildtype) which could suggest the second loop has a C5a binding site. However, there was no signal transduction with Ch11, and an alternative view suggested was that the second loop is indirectly involved in binding through correct positioning of the transmembrane helixes to allow C5a binding to a TM domain to effect signal transduction. Construct Ch14 (C3aR 2nd loop on C5aR) lost C5a binding and most signal transduction. Crass concluded that this result was best explained by disruption to the TM helix bundle through an indirect effect by the 2nd loop – the size of the loop being the critical factor because this affects the positioning of the TM helixes i.e. the 2nd loop is not a direct binding site for C5a. For C3aR, Crass concluded that ligand (C3a) binding to the 2nd loop was less likely an explanation for the results observed with various chimeric receptor constructs because of poor sequence homology between different species. A similar conclusion could be made for C5aR given sequence divergence found in the 2nd loop. Crass provides no compelling reason to target the 2nd loop; instead, the results presented in Crass confirm the importance of the N-terminus of C5aR for high affinity binding of C5a.

In 1999 the accepted model for C5a/C5aR signalling (Crass, Introduction) was the N-terminus of C5aR binds core residues of C5a providing ~50% of the overall binding energy. The C-terminus of C5a then binds a second site in C5aR spanning several residues scattered among the extracellular loops and TM helices. Nothing in the results presented by Crass suggests that this model is not correct.

There is no disclosure in Crass of antibodies generated against the extracellular loops of C5aR.

Cain

The Office Action stated that Cain teaches that two of the extracellular loops, namely the second and third, and the N-terminal domain, are essential for C5a binding.

Cain describes mutations to certain residues in the first extracellular loop of C5aR. These mutations increased the affinity of C5a for the receptor, suggesting the first loop is important in ligand binding (contrary to data from Pease). Cain states that the data **cannot distinguish** between (i) the residues in the first loop having direct contact with the C5a, and (ii) the mutations changing the conformation of the ligand binding pocket. Cain also makes the point that various peptide agonists, antagonists, C5a and C5adesArg (which have different modes of interacting with C5aR) are all differentially affected by mutations in the first loop.

The Office Action quotes Cain as teaching that the N-terminus and second and third loops are essential. This "teaching" is actually Cain citing Pease; see page 1572, left hand column, second paragraph. The conclusions from Pease are not, however, as black and white as Cain's citation suggests (see discussion of Pease, above). Cain also goes onto say that the N-terminus of C5aR is required for high affinity binding of C5a.

There is no disclosure in Cain of antibodies generated against the extracellular loops of C5aR.

Pease, Crass, and Cain all describe studies which look at specific regions of C5aR (by generation of chimeric receptor molecules or mutation analysis) in order to elucidate binding modes for ligands such as C5a. Pease, Crass, and Cain highlight the importance of the binding of ligands to the N-terminal domain. The conclusions made about the importance of other extracellular loops vary from generally inconsistent or inconclusive. None of Pease, Crass, and Cain discloses or suggests antibodies directed against extracellular loops of C5aR.

The only citations that describe anti-C5aR antibodies are Morgan and Oppermann. Morgan describes only antibodies against the N-terminal domain. Oppermann describes polyclonal antibodies against all extracellular loops, but clearly concludes that only antibodies against the N-terminal domain inhibit binding of C5a.

Accordingly, the overwhelming suggestion from these combined references is that the N-terminal domain is most important for ligand binding. A person of skill in the art faced with the problem of designing an antibody which inhibits binding of C5a to C5aR, and given the cited art, would therefore choose to develop antibodies against the N-terminal domain. Indeed, Oppermann, the only citation which discloses and compares antibodies to all extracellular loops, makes it clear that antibodies directed to extracellular loops another than the N-terminal domain are likely to be ineffective.

Finally, the examiner states: "The burden is on the applicant to establish a patentable distinction between the antagonistic antibodies that bind second extracellular loop of C5a receptor and the epitope specificity of the claims 7F3, 6C12 and 12D4 antibodies." However as explained above, the only antibodies described in the cited art are monoclonal antibodies directed against the N-terminal domain (Morgan) and ineffective polyclonal antibodies directed against the other extracellular loops (Oppermann). The cited art does not disclose any antibodies against an extracellular loop other than the N-terminal domain which are effective in inhibiting binding of C5a to C5aR.

Conclusion as to the rejection under 35 U.S.C. §103(a)

Applicant submits that the rejection of claims 1-9, 25-28, and 33-39 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-032.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 14, 2010

By: /Carol L. Francis, Reg. No. 36,513/
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Enclosure(s): Statement of Availability of Biological Deposit

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